

**Topic:** Laboratory Work-up of Lymphoma in Adults**Date:** November 11, 2020

Why was the guideline developed?

The diagnostic workup of lymphoma continues to evolve rapidly as experience and discovery leads to the addition of new clinicopathologic entities and techniques to differentiate them. The optimal clinically effective, efficient, and cost-effective approach to diagnosis that is safe for patients can be elusive, in both community-based and academic practice. This guideline was developed to reduce variation and uncertainty related to the workup of suspected lymphomas, using the available evidence-base to develop recommendations for appropriate evaluative processes.

Can you provide a definition of an ancillary studies?

Ancillary studies covered in this guideline include immunohistochemistry (IHC) and immunocytochemistry, fluorescence in situ hybridization (FISH), mutational analysis, and flow cytometry routinely performed in the pathology laboratories to support a definitive diagnosis of lymphoma.

In my institution, a fine needle aspiration (FNA) with an on-site evaluation is used for ruling out a lymphoma for patients who present lymphadenopathy. The guideline does not recommend this as an initial step. Why is that?

The guideline does not recommend the use of FNA cytomorphology alone to investigate individuals with suspected lymphoma. The studies reviewed documented a low sensitivity and negative predictive value when FNA is used alone. Additionally, FNA alone is associated with a high rate of incorrect classification of lymphoma subtype. However, this guideline does not categorically exclude the FNA approach if ancillary testing including flow cytometry and IHC is applied concurrently.

Can you provide examples where an FNA would be preferred over excisional biopsy?

Multiple factors may influence the decision between an initial FNA approach over a large volume biopsy. Such considerations include the relative probability of non-hematopoietic malignancy (which might be associated with greater diagnostic yield with an FNA approach), difficult-to-access lesions with limited other options of low procedural risk, or a narrow diagnostic question (using FNA as an assessment tool to evaluate for relapsed lymphoma). Such considerations should ideally be discussed between clinical care providers, pathologists, and patients in a shared decision-making process.

What lymphoma types are best identified using a bone marrow biopsy for primary diagnosis?

For certain lymphoma types such as splenic low-grade lymphomas or lymphoplasmacytic lymphomas (LPL), bone marrow biopsy may be preferred over more invasive surgical methods with high patient risk (e.g. splenectomy). For other lymphoma types, no recommendation is rendered, acknowledging that in a small number of select patients a diagnosis of lymphoma may be rendered on bone marrow biopsy with appropriate ancillary testing.



Cerebrospinal fluid (CSF) samples are often not cellular enough to be ordered for ancillary testing. Is there a recommendation for a minimum CSF sample for the diagnosis of lymphoma?

The guideline's evidence-base did not establish a minimum CSF sample required for lymphoma diagnosis. There are potentially studies that address this question that may have preceded the timeframe established for the literature review. These studies typically emphasized the importance of multiple, larger volume CSF samples to diagnose central nervous system involvement of lymphoma, and the guideline highlights that these were mainly completed in an era before the availability of ancillary tests that might improve diagnostic yield. The expert panel ultimately considered this question out of scope for this guideline.

Molecular and genomic tests should be ordered for subclassification. Why does the guideline recommend against up front testing on molecular and genomic tests?

The large majority of lymphomas are obviously malignant based on morphologic features, eliminating the necessity of proving clonality. When necessary to prove clonality, B-cell clonality is commonly established with flow cytometric analysis, without additional value of immunoglobulin gene rearrangement in most cases. Similarly, flow cytometry is applicable to documenting the presence of overtly aberrant T-cell populations, and also presently has the ability to directly demonstrate clonality in specific populations. With a low pre-test probability of T-cell lymphoma, the number of false positive T-cell receptor gene rearrangements may exceed the number of true, "biologic" positive rearrangements since non-malignant clonal T-cell expansions have been reported in up to 10% of B-cell lymphomas and 13% of reactive lymphadenopathies.

Why is a strength of recommendation considered "strong" when evidence is "low" or "very low"?

During the guideline development, the evidence-base was found to be of weak or lower quality for a majority of the recommendations. Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for guideline development, the quality of evidence is one important consideration to inform the strength of recommendation but is also evaluated along with the considered judgement of the expert panel. This formal and transparent process involves weighing the benefits and harms of each potential recommendation, in addition to considering values such as health equity, resource utilization, and acceptability to key stakeholders. For most of the strong recommendations based on low strength of evidence, it was determined that providing a recommendation for the opposite action could result in substantial harms to patients.

How will the guideline be enforced?

As with any clinical evidence-based guideline, following the recommendations is not mandatory. Recommendations may be incorporated into future versions of the CAP Laboratory Accreditation Program (LAP) checklists; however, they are not currently required by LAP or any regulatory or accrediting agency. It is only highly encouraged that clinicians and laboratories adopt these recommendations, as appropriate for their clinical settings.